Lysosomal "Storage" Disorders

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Disclosures:

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Flights and accommodation to this conference kindly paid for by Sanofi Genzyme

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Background

Heterogeneous group of genetic disorders (AR / XL)
> 50 disorders
Prevalence ± 1 in 7000

Lysosomal function largely processing and degrading biomolecules

Most LSD’s due to deficient lysosomal enzyme function → substrate accumulation → cell dysfunction but complex!

Other mechanisms - abnormal protein folding, abnormal transport etc.
Clinical Presentation

Very variable “spectrum”

Typically slowly progressive

Onset anytime from prenatal to late adulthood

Variable expression in part related to residual enzyme activity

Organs most involved - brain, connective tissue, eye and heart
Common clinical presentations

Non immune fetal hydrops

Neurological regression

“Storage phenotype” - macrocephaly, coarse facies, visceromegaly, dysotosis multiplex

Cardiomyopathy

Skeletal or joint symptoms / signs
Dysostosis multiplex

Paddle shaped ribs, and short, thickened clavicles

2A

2B

anterior beaking of the lumbar vertebrae (posterior scalloping)

tubular bones - thickened cortices, irregular metaphyses, underdeveloped epiphyses phalanges shortened and trapezoidal in shape
Diagnosis

Screen for metabolites
  False + and false -
  Urine / blood

Diagnose with specific enzyme assay
  Lymphocytes
  Fibroblasts
  Amniocytes

Confirm / family management with molecular genetic analysis
  Some genotype phenotype correlations but limited
  Increasingly important
Management principles

Index of suspicion!

Surveillance and supportive management

Genetic counseling

Specific therapy
  Decrease substrate
  Reduce degradation
  Replace enzyme
  Replace “factory”
  Gene therapy
The pathogenetic cascade of lysosomal storage diseases and the therapeutic approaches to treating these disorders.
Mucopolysaccharidoses

Characterised by abnormal metabolism of glycosaminoglycans (*urinary screening test*)

Autosomal recessive except MPS II X-linked

Type I - IX (no V or VIII....)

Subtypes

Variable clinical expression in single gene (MPS I)
Variable cause with same phenotype (MPS III and IV)

Some LSD’s responsive to ERT
MPS I
Hurler /Hurler-Scheie/ Scheie syndrome

**Prenatal**
Hydrops fetalis

**Severe**
1-2 yrs of age (though retrospectively ? before 1) hernias, gradual coarsening of features with hypotonia. gibbus / kyphosis, organomegaly, macroglossia hearing dysfunction, *cloudy corneas* (retina/ glaucoma) progressive skeletal changes , cardiac involvement, (valves and CMO), airway obstruction , and intellectual disability, hydrocephalus, CTS..

**Attenuated**
Onset mid childhood with focus on bone and joint symptoms Neurological function normal to mild ID Cardiac valvular disease and hearing loss common
Management

Supportive

Airway
Heart
Mobility
Hearing
Vision
Anaesthetics

TEAM BEST!!
Treatment

**ERT**

Blood Brain Barrier a problem

Improvement in growth, airway, joints, facial coarseness, mobility, liver size and quality of life

Role in attenuated form is well established
Severe form + HSCT

Early diagnosis important but prediction of severity not always clear

If family history phenotype easier but with newborn screening may be harder

Not generally recommended in severe MPS 1 with established developmental delay….. but many co-morbidities and may still improve quality of life
HCST reduces facial coarseness, and hepatosplenomegaly, improves hearing, and maintains normal heart function skeletal manifestations and corneal clouding progress

“optimise’ condition with period of ERT before HSCT and may have some benefit later from ERT with certain symptoms that evolve post transplant

before significant developmental delay appears to slow the course of cognitive decline

“Gold standard” in severe (I-H) patients less than 2.5yrs
MPS II
Hunter syndrome

**Severe**
Very similar to MPS I
Slightly later onset
Early joint stiffening
Clear corneas usually

**Attenuated**
Typically no or minimal neurological dysfunction
May have significant systemic effects
Joints / bone presentation
Supportive
As for MPS I

Specific
ERT
Largely used in attenuated form
Does not cross BBB
Improvement in effort tolerance and FVC/visceromegaly
? Improved airway, joints, facial coarseness, mobility, QOL
Individualise in more severe patients (early diagnosis ??)

“enzyme replacement therapy with idursulfase is effective in relation to functional capacity (distance walked in six minutes and forced vital capacity), liver and spleen volumes and urine glycosaminoglycan excretion in people with mucopolysaccharidosis type II compared with placebo”
Cochrane Database Syst Rev. 2016 Feb Enzyme replacement therapy with idursulfase for mucopolysaccharidosis type II (Hunter syndrome).
da Silva EM1, Strufaldi MW, Andriolo RB, Silva LA.

HCST
Little data
Uncertain benefit - may stabilise ? No CNS effect
MPS IV
Morquio syndrome Type A /B

“Skeletal “
Usually normal growth in 1st year
Fall off in growth with disproportion and deformity
  Short trunk “dwarfism”

No CNS dysfunction (unless secondary)

Joints lax  NB Odontoid hypoplasia and unstable CCJ

Minimal coarsening and systemic features
  corneal opacity – slit lamp
  hernias, cardiac valve abnormalities, hepatomegaly

Treatment
Supportive – stabilise neck!
ERT  for IV A – improved walk / QOL ? Effect on bones
MPS VI
Maroteaux Lamy syndrome

**Severe**
From 1\(^{st}\) year of life to adulthood
Skeletal manifestations often first
Facial coarsening follows
Joints, airway and heart all involved
Frequent ear and chest infections
Corneal clouding, glaucoma.. Retina
Hydrocephalus , CTS and myelopathy

**Attenuated / Mild**
Often very slowly progressive over many decades
Management

Supportive
Often need tracheostomy for UAO in severe type

Specific
ERT
Considered first line therapy
Does not cross BBB
Improvement in improved walking endurance and stair climbing
? ?Improved airway, joints , visceromegaly, heart (LV)

HCST
Improves facial dysmorphism and heart
Uncertain benefit on bones - may improve joint mobility
Glycogen storage disorder Type II
Pompe Disease

*Infantile*
CLASSIC:— 1\textsuperscript{st} month or 2 floppy, feeding, respiratory and cardiac failure / LVOTO
ATYPICAL – later 1\textsuperscript{st} year or 2… less cardiac more weakness

*Late onset*
Muscle weakness NB proximal and respiratory
*(CK can be normal)*

*Treatment*
Enzyme diagnosis *urgently*..

Supportive – careful cardiac!!

ERT
Pompe Disease in Infants: Improving the Prognosis by Newborn Screening and Early Treatment

Yin-Hsiu Chien, Ni-Chung Lee, Beth L. Thurberg, Shu-Chuan Chiang, Xiaokui Kate Zhang, Joan Keutzer, Ai-Chu Huang, Mei-Hwan Wu, Pei-Hsin Huang, Fuu-Jen Tsai, Yuan-Tsong Chen, Wuh-Liang Hwu

Pediatrics Dec 2009, 124 (6) e1116-e1125;

Pompe Disease: Early Diagnosis and Early Treatment Make a Difference

Chien, Yin-Hsiu et al.

Pediatrics & Neonatology, Volume 54, Issue 4, 219 - 227
Gaucher Disease

**Type 1**
Bone disease (osteopenia, focal lytic / sclerotic lesions/osteonecrosis), Hepatosplenomegaly, anaemia and thrombocytopenia
Lung disease **NO** primary central nervous system disease

**Type 2 and 3**
+ CNS disease

**Cardiovascular**
Calcification of the mitral and aortic valves, mild splenomegaly, corneal opacities, and supranuclear ophthalmoplegia (**homozygous D409H allele**)

**Perinatal lethal**
Non immune hydrops
Treatment

Enzyme diagnosis

Supportive

Specific therapy

ERT
Effects on bone disease, visceral involvement and QOL
Limited effect on CNS manifestations but may stabilize

Substrate reduction

Chaperone Rx

BMT...largely replaced by ERT
Photographs courtesy of Sanofi Genzyme
Fabry Disease

X-linked but males and females affected
Females ? milder / reduced penetrance
Enzyme diagnosis in males / molecular diagnosis in females

**Childhood**
*Acroparasthesias* and Abdominal pain
Hypohidrosis
*Boys ~7  Girls ~9*

**Adulthood**
Renal disease
proteinuria -> end stage renal disease
Cardiovascular disease
CMO, valvar disease, rhythm disturbance
Stroke
Angiokeratomas

Cornea verticillata
Treatment

Supportive

Pain, renal, cardiac

ERT

Improves symptoms, cardiac function
“Uncertain” long term effect on renal and cerebrovascular disease?
Significantly better outcome for treated registry patients than historical ‘controls’

“Trials comparing enzyme replacement therapy to placebo show significant improvement with enzyme replacement therapy in regard to microvascular endothelial deposits of globotriaosylceramide and in pain-related quality of life”


? timing of treatment important
? subtype of disease important
Genetic counselling

**Autosomal recessive**
- Parents unaffected
- Often no family history!
- 25% risk for siblings
- e.g. Gaucher disease

**X linked - recessive**
- Males affected
- Female carriers
- e.g. MPS II

**X linked – “semi” dominant**
- Males and females affected
- Females milder
- All daughters of affected man “carriers”
- e.g. Fabry disease
So to the future…

Therapy options

( none curative yet)

ERT
HSCT
Substrate reduction
Chaperone therapy

New approaches – Intrathecal / Intrarticular ERT
Better understanding of cell biology and pathophysiology

Gene therapy not quite there but trials in MPS III + other LSD’s

Prenatal / preimplantation genetic diagnosis
Must know what you are looking for – DNA on affected child
Early therapy is likely to be key...

Recognition and reliable diagnosis
Newborn screening
Genotype phenotype correlations

Still many unanswered questions

More data needed
RCT not that easy once medication registered
Registry participation important

Thank you.